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LENNART SCHOTTE

Studies on sulphur compounds related to glutaric and pimelic acid with special reference to the 1,2-dithiolane system

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Studies on Sulphur Compounds Related to Glutaric and Pimelic Acid with Special Reference to the 1,2-Dithiolane System

INAUGURAL DISSERTATION

BY

LENNART SCHOTTE

FIL. LIC., VÄRML.

BY DUE PERMISSION OF THE PHILOSOPHICAL FACULTY OF THE UNIVERSITY OF UPPSALA, TO BE PUBLICLY DISCUSSED IN THE LECTURE HALL OF THE INSTITUTE OF CHEMISTRY, APRIL 28, 1956, AT 10 A.M., FOR THE DEGREE OF DOCTOR OF PHILOSOPHY. IN ADDITION TO THIS SURVEY THE PAPERS NUMBERED 1–11 IN THE LIST OF REFERENCES WILL BE PUBLICLY DISCUSSED.

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Studies on sulphur compounds related to glutaric and pimelic acid with special reference to the 1,2-dithiolane system

By Lennart Schotte

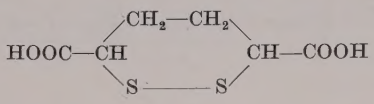
With 11 figures in the text

Introduction

A thorough study of sulphur compounds related to dicarboxylic acids was first performed by Fredga, who examined the adipic acid series in the years 1937–1938 (12–14). Thus the diastereomers of α,α′-dimercaptoadipic acid and their cyclic oxidation products, *racem-* and *meso*-1,2-dithiane-3,6-dicarboxylic acid (I), were characterized (13, 14). The cyclic disulphides are of special interest since valuable information is obtained about the properties of the S–S group. As the compounds in question contain two similar asymmetric centres, the influence of steric effects may also be studied. Supplementary information may be obtained by comparison with the corresponding selenium compounds (15–18).

The purpose of this and previously reported investigations (1–11) has been to pursue the work outlined above and extend it to glutaric and pimelic acid. It was soon found that the related disulphides were most interesting and in particular those with five-membered rings, derived from α,α′-dimercaptoglutaric acid. Special study has therefore been devoted to this 1,2-dithiolane (1,2-dithiacyclopentane) system. Difficulties, which were encountered in the preparations, have, however, necessitated some digressive studies. The properties of the cyclic disulphides have been elucidated mainly by physico-chemical methods, which include a spectrochemical investigation on disulphides in general.

The expectations of Fredga (14) as to the importance of a closer study of cyclic disulphides have been fully realized by the discovery and synthesis of 6-thioctic acid (6,8-dithio-*n*-octanoic acid or α-lipoic acid) (II) which contains the 1,2-dithiolane ring (19–28). It has been found that this substance is active in the oxidative decarboxylation of pyruvate to active acetyl groups (29–33). Calvin and co-workers have furthermore advanced a hypothesis that the disulphide acid itself is involved in the conversion of the electromagnetic energy of quanta into chemical bond energy (34–36). The available energy of the photochemically exited chlorophyll molecule should in such a case start photosynthesis by splitting the disulphide bond into a biradical. As this would be possible only with a sufficiently high strain energy in the 1,2-dithiolane part of the 6-thioctic acid molecule, it has become a matter of importance to study the chemistry and physics of the 1,2-



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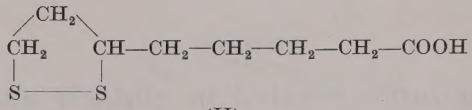

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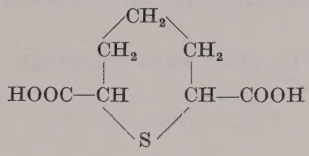

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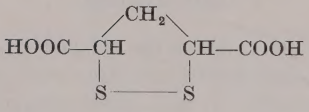

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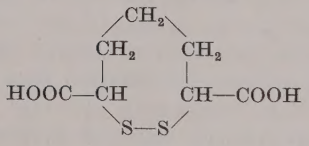

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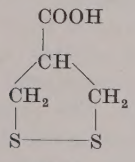

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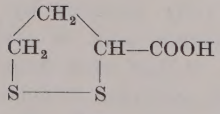

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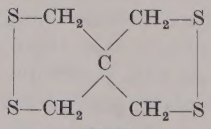


(VIII)

dithiolane derivatives. The reactivity of the system is directly connected with the geometry of the S–S linkage, which will be discussed later on. It should be noted here that CALVIN and his co-workers tried to calculate the strain from spectroscopic studies, from purely structural considerations together with some measured single bond rotational barriers (conformation analysis), and from kinetic studies of the equilibrium between benzyl mercaptan and 1,2-dithiolane. The results have been discussed by SUNNER (37, 38) and compared to his own, obtained in a more direct way by calorimetric experiments. SUNNER found a lower value for the strain energy of 1,2-dithiolane than those reported by CALVIN. The method involving spectroscopic studies has been particularly criticized by SUNNER, who arrives at the conclusion that the hypothesis of CALVIN about the second step of the photosynthesis cannot be correct, in any case in its original version (38). As the reference cited (38) contains a valuable review of the chemistry and energetics of 6-thioctic acid no further discussion of the matter will be given here. The problem cannot be regarded as definitely settled until the chemistry of the 1,2-dithiolane ring is known in detail.

Discussion of methods of preparation

The α,α′-dibromo-dicarboxylic acids are in general starting materials for the synthesis of related mercaptans, sulphides and disulphides. It is thus essential to know the configuration of the diastereomers to be used. In the case of α,α′-dibromoglutaric acid the assignments given (39, 40) are based only upon assumptions and so a closer investigation seemed justified (1). It was found that methods involving ionization of the carboxylic groups, e.g. resolution of the presumptive racemic acid, cannot be used for the establishment of configuration because of the rapid elimination of hydrogen bromide with lactone formation. The diastereomers were then examined as to their infrared absorption in the sodium chloride prism region in an attempt to correlate the results to recently established relationships between configuration and infrared absorption (41–45). The infrared approach to stereochemical problems in general has proved promising and especially in the succinic acid series significant effects of different spatial distribution have been observed. The results obtained from this spectral method certainly strengthen the hitherto accepted assumption about the configuration of the diastereomers of α,α′-dibromoglutaric acid, but the effects are small and should not be regarded as incontrovertible (1). Only one of the corresponding α,α′-dichloro acids is hitherto known (46).

A method of separation has been described for the diastereomers of α,α′-dibromopimelic acid (2). Conclusive evidence as to the configurations has been presented by the optical resolution of the low-melting acid. It has also been possible to characterize the enanthiomorphs (2).

Although it is somewhat beyond the scope of this subject, it may be justified to call attention to the tables in reference (2), which illustrate the melting points of the diastereomers of homologous α,α′-dimethyl- and α,α′-dibromo-dicarboxylic acids (2: Table 1) and the optical activities of some enanthiomorphs within the series of α,α′-dibromo acids (2: Table 2). It should be noted that in general the meso isomers are the high-melting acids but that deviation from the apparent regularity is found for α,α′-dimethylglutaric acid. The melting point curve of the antipodes of this acid, however, reveals the existence of a racemic compound of great stability, melting about 60° higher than the active forms (the meso acid also has a higher melting

point than the active acids). It may be concluded that a comparison between the melting points of meso and active acids should be more significant.

A survey of different methods for the preparation of α,α′-dimercapto-dicarboxylic acids is given in reference (3). The pimelic acid derivatives are obtained by hydrolysis of the corresponding ethyl xanthates (4) whereas the method involving intermediate formation of thiolesters must be used in the case of α,α′-dimercaptoglutaric acid (3, 5). The complications in the glutaric acid series are discussed in reference (5) and will also be considered briefly below. It may be mentioned that unsuccessful attempts have been made to prepare 1,3-bis-ethylxanthogen-propane-tetracarboxylic acid-1,1,3,3 which should be easily decarboxylated to the glutaric acid derivative. Xanthogen substituted malonic acids are known to be rather unstable (47).

The sulphides related to the diastereomers of α,α′-dibromopimelic acid, *cis*-(*meso*)- and *trans*-(*racem*)-tetrahydrothiapyran-2,6-dicarboxylic acid (III), have been prepared in reactions with sodium sulphide (6). These replacements proceed without racem ⇌ meso rearrangements.

The disulphides, *racem*-1,2-dithiolane-3,5-dicarboxylic acid (IV) and the diastereomers of 1,2-dithiepane-3,7-dicarboxylic acid (1,2-dithiacycloheptane-3,7-dicarboxylic acid) (V) have been synthesized from the related dibromo acids and sodium disulphide or by oxidation of the corresponding dimercapto acids (3–5, 48, 49). The oxidizing agents used are hydrogen peroxide, oxygen and iodine. For the pimelic acid series iodine has proved to be the best reagent (4), whereas no differences were found for the oxidations of *racem*-α,α′-dimercaptoglutaric acid (5). A hypothetical method for synthesis of the 1,2-dithiolane derivatives from diethyl bromo malonate and potassium disulphide with subsequent ring closure by means of formaldehyde, followed by hydrolysis and decarboxylation could be excluded due to the fact that alkali disulphides rapidly reduce diethyl bromo malonate to diethyl malonate (cf. 47).

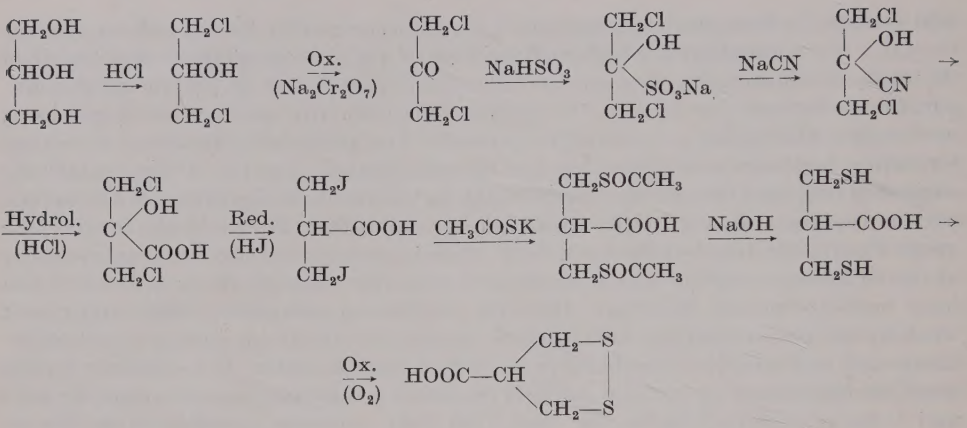
There are some remarks which should be made in connection with the methods of preparation reported above. In accordance with the observations of FREDGA as regards the alkali disulphide (12) and in particular the diselenide (15) reactions with α,α′-dibromoadipic acid it has been found that in the above mentioned synthesis of (V) some monosulphide acid (III) is also formed. Thus, both the meso acids were isolated (4, 49) and the same kind of reaction is likely also for the racemic series, where the solubility conditions, however, have rendered a separation difficult. If this result is connected with the fact that during syntheses of 1,2-dithiepane derivatives, polymeric substances are always by-products (the amounts can be reduced at high dilution), the nature of the replacements in the cyclization reactions may be rather well interpreted. No racem ⇌ meso conversions are observed and thus it seems justified to conclude that after the first replacement at one of the asymmetric centres the reaction may proceed either with ring closure to monomer disulphide, with ring closure and separation of sulphur to monosulphide or by forming disulphides of polymeric character. It should be pointed out that no stable intermediate with coordinatedly linked sulphur has been observed. Reasons for the improbability of branched sulphur chains are given in reference (7) (see also below). The correlation between the above mentioned modes of reaction and the steric conditions is well illustrated by the fact that the two ring closure alternatives occur in the adipic acid series, where the related disulphide is six- and the sulphide five-membered. All the reaction possibilities are observed for the pimelic acid derivatives, where the disulphide ring is larger (seven-membered).

The above considerations for the disulphide reactions are not true for the glutaric

acid system. In fact, steric conversions seem to occur readily for the sulphur derivatives (5). It is found that the high-melting form of α,α′-dibromoglutaric acid (ascribed the meso configuration) gives the racemic disulphide (5, 48). If the accepted configuration is correct (see above), the cyclization reaction in question must involve a mechanism which allows steric rearrangements. As a pronounced tendency to lactone formation has been established for α,α′-dibromoglutaric acid (3), it was tentatively suggested (48) that the reaction could imply an intermediate formation of a γ-lactone with subsequent attack of the disulphide group within the molecule to give the cyclic disulphide dicarboxylic acid. Such a mechanism should involve two inversions at one of the asymmetric centres and one at the other, thus resulting in a conversion from meso to racemic structure. However, studies on molecular models and recent work by the present author on the attack by sulphur-containing groups on γ-butyrolactone (8) indicate the improbability of such an interpretation. It is certainly known from the difference in lactone stability between γ-butyrolactone-γ-carboxylic acid and γ-butyrolactone-β-carboxylic acid (50) that carboxy substitution in the γ-position considerably favours ring opening but nevertheless the steric arrangements and the reaction conditions seem inconsistent with the assumption of a lactone intermediate. The conversion can surely be best accounted for by assuming the replacements to proceed according to S_1 and S_2 mechanisms with preliminary retention and then inversion of configuration. As the reactions under discussion for the adipic and pimelic acid obviously involve S_2 substitutions only (see above), the question arises whether the observed effect is characteristic for the glutaric acid system or should be connected with the strained disulphide ring to be formed. No unambigous answer can be given, but attention is called to the intense investigation of the reaction between the diastereomers of dimethyl α,α′-dibromoglutarate and alkali thiolacetate (5). Racem ⇌ meso rearrangements during the hydrolysis render reliable conclusions about the substitutions impossible. The fact that it has not been possible to isolate any *meso*-1,2-dithiolane-3,5-dicarboxylic acid (see below) makes the interpretation of the reaction mechanism rather difficult (5). Regardless of the nature of the mechanism it should be remembered that the competitive reactions in the disulphide preparations are different for the glutaric and pimelic acids: for glutaric acid lactonization, for pimelic acid formation of monosulphide and polymers.

With regard to the discussion in reference (8) about the different modes of attack of mercaptides and alkoxides on γ-butyrolactone it should be mentioned that REPPE has described some reactions of γ-butyrolactone in a recent paper (51). He states that alkoxides cause ring cleavage at the alkyl carbon-oxygen bond in conformity to the results of FITTIG and STRÖM in 1892 (52). The work of the latter authors has, however, been doubted by SPENCER and WRIGHT (53), who arrived at the opposite conclusion (acyl carbon-oxygen bond fission) after a very careful investigation under proper conditions. REPPE does not seem to have been aware of this work. The assumption of the present author in reference (8) that both acyl and alkyl attack occur simultaneously but with different rate should perhaps be stressed. However, the reaction products of REPPE might be the result of secondary reactions under the conditions employed.

Finally it may be mentioned that the 4-substituted 1,2-dithiolanes, the spectrochemical investigation of which is reported in reference (9), were prepared according to BACKER and co-workers (54–56). 1,2-Dithiolane-4-carboxylic acid (VI), possibly the disulphide existing in asparagus (cf. JANSEN (57)), has been synthesized according to the following scheme (58)



(VI)

Dimercapto acids

It should be pointed out that α,α′-dimercaptosuccinic acid cannot be prepared by the methods discussed above. OWEN and SULTANBAWA (59) have, however, described the preparation of a mixture of the diastereomers by addition of thiolacetic acid to acetylenedicarboxylic acid and subsequent acid hydrolysis of the bis-acetyl compound formed. No separation of the isomers was performed. Special attention may be called to the formation of α-xanthogen-γ-butyrolactone-γ-carboxylic acid in reactions between α,α′-dibromoglutaric acid and potassium ethyl xanthate, as interesting effects on the infrared absorption are found for the acid salt in particular, for the lactone acid and the neutral salt (3). The homologous α,α′-dimercapto-dicarboxylic acids are collected in Table 1.

The enanthiomorphs of α,α′-dimercaptopimelic acid have not yet been prepared. It should be noted that the racemic acid is the high-melting isomer, whereas the reverse is true for the related dibromo (2) and cyclic disulphide derivatives (4). α,α′-Dimercaptoglutaric acid is found to decompose readily upon heating with the formation of lactone or/and thiolactone. An account of the reactions of some thiolactones is given by SCHJÅNBERG (60).

Table 1. Homologous α,α′-dimercapto-dicarboxylic acids.

Derivative of	M.p.			Ref.
	Meso form	Racem form	Enanthiomorphs	
Glutaric acid	—	135° –136°(141°)	84° – 86°(91°)	(5)
Adipic acid	188°	111.5°–112.5°	119.5°–120.5°	(14)
Pimelic acid	81°–83°	106° –107°	—	(4)

Sulphide acids

No investigation of the glutaric acid series has been made in this respect due to the properties which can be postulated for the four-membered cyclic sulphide acids on the basis of other experiments. The adipic and pimelic acid derivatives are compared in Table 2.

Table 2. Some cyclic sulphide dicarboxylic acids.

Substance	M.p.			Ref.
	Meso (*cis*) form	Racem (*trans*) form	Enanthiomorphs	
Thiophane-2,5-dicarboxylic acid	144°–145°	165°–166°	179°–180°	(12)
Tetrahydrothiapyran-2,6-dicarboxylic acid . . .	210°–211°	148°–149°	—	(6)

The characteristics and reactions of the diastereomers of tetrahydrothiapyran-2,6-dicarboxylic acid are described in reference (6). The preliminary optical resolution of the racemic isomer has not been further pursued. It is of interest to note that steric conversions occur upon hydrolysis of the pure esters of the diastereomers, whereas the cyclization reaction proceeds without racem ⇌ meso rearrangements for acid as well as ester (3). The same is true when the thiophane derivatives are formed from the diastereomers of α,α′-dibromoadipic acid (or the dimethyl esters) and sodium hydrosulphide (3); this reaction involves rapid alkylation of a mercapto group with ring closure (cf. also 61).

Disulphide acids

The cyclic disulphide acids related to glutaric, adipic and pimelic acid are collected in Table 3.

Two mono-carboxylic acid 1,2-dithiolane derivatives are also known. 1,2-Dithiolane-3-carboxylic acid (VII), m.p. 81°–82° (147°), has been described by CLAESON (62); 1,2-dithiolane-4-carboxylic acid (VI), m.p. 76.5°–77.5°, has recently been prepared by the present author and STRÖM (58) (see above).

Table 3. Some cyclic disulphide dicarboxylic acids.

Substance	M.p.			Ref.
	Meso form	Racem form	Enanthiomorphs	
1,2-Dithiolane-3,5-dicarboxylic acid	—	194°–195°	185°–187°	(5)
1,2-Dithiane-3,6-dicarboxylic acid	199°	*c.* 270° (d.)	*c.* 257°	(14)
1,2-Dithiepane-3,7-dicarboxylic acid	191°–193°	171°–173°	—	(4)

In spite of several attempts it has not been possible to prepare *meso*-1,2-dithiolane-3,5-dicarboxylic acid. This may suggest an appreciable instability of the compound but it is also likely that the steric conditions are unfavourable for ring closure. A readily occurring rearrangement to the racemic isomer or combinations of the different factors may account for the experimental result. The first two suggestions seem consistent with the observations of FREDGA (17, 18) as regards the preparation of *meso*-1,2-diselenane-3,6-dicarboxylic acid (*meso*-cyclotetramethylene-diselenide-3,6-dicarboxylic acid). Amorphous products of a polymeric nature have been found as by-products; it is very difficult to get the monomer pure and even the pure meso acid shows a pronounced tendency for polymerization. In this respect attention is called to the fact that a definite polymeric disulphide acid related to *meso*-1,2-dithiepane-3,7-dicarboxylic acid was isolated by the present author under certain conditions (4). A further study of this polymer could perhaps give information about the behaviour of larger disulphide rings. The disulphide related to suberic acid contains an eight-membered ring but preliminary work by FREDGA has given only polymeric products (63).

The resolution of racem-(V) has not yet been completed due to lack of substances. The preliminary tests have, however, indicated rather high molecular rotation for the enanthiomorphs (4).

1,2-Dithiolane-4-carboxylic acid (VI) is of a special interest, as the related dimercaptan has been isolated from asparagus (57). JANSEN qualitatively showed the presence of disulphide and mercaptan in asparagus juice but attempts at isolation gave only polymeric disulphide products. Reduction of the polymer gave a dimercaptan which was characterized as β,β'-dimercapto-*iso*-butyric acid. These results might suggest that the disulphide present in asparagus is really of polymeric character, but the experiences of the present author in the preparation of (VI) clearly shows that not even the conditions used by JANSEN were mild enough to ensure the isolation of a possible monomer. The 1,2-dithiolane system is reactive and cleavage of the S–S bond with formation of linear polymers readily occurs. As a consequence it seems reasonable to assume the presence of (VI) in asparagus and it will be examined later to find out if the occurrence of the reactive ring system is important for the biochemical processes in the rapidly growing asparagus.

Properties of disulphides

General remarks

For a complete understanding of many of the disulphide properties it is essential to know the steric arrangement of the bonds around the S–S group. The *s* electron pair is spherically distributed about the nucleus and the *p* pairs are on the 90° axes. Thus the distribution leads to a very interesting spatial configuration for disulphides. There are two symmetrical energy minima for rotation around an S–S linkage and the dihedral (azimuthal) angle is between 90° and 100° (the angle between the two S–S–C planes). The rotational barrier corresponds to at least 10 kcal. as determined by careful spectroscopic studies on dimethyl disulphide (64) and diethyl disulphide (65). Energy maxima are found for the trans- and cis-position, of which the latter with a dihedral angle of 0° may from steric reasons be expected to have somewhat higher energy (66). For 2,3,4-trithia-*n*-pentane (67) a dihedral angle of 93° is reported, whereas PAULING found 102° for the ordinary S_8 molecule (66).

It seems difficult to account for the rotational barrier but it may probably be connected with the tendency for the unshared p electrons on the two sulphur atoms to overlap when the dihedral angle is 0° or 180° (cf. 35). This overlap must then result in coulombic repulsion between non-bonding electron pairs and hence a potential barrier at the coplanar position with a minimum near 90° (68).

For comparison with related groups it should be mentioned that quantum mechanical calculations have established a dihedral angle of about 100° for the peroxide bond in hydrogen peroxide (69). There exists also an energy barrier, which must be passed to permit rotation from this angle. ROGERS and CAMPBELL have made dipole moment measurements (70) on related aliphatic peroxides, disulphides and diselenides, from which conclusions are drawn about the dihedral angles.

From the above considerations about the stabilized skew configuration of linear disulphides (for a representative figure, see (38)) it can be readily understood that special properties must be attributed to five-membered and to some extent also to six-membered cyclic disulphides. This is well illustrated by the work of AFFLECK and DOUGHERTY (71) on the preparation and relative reactivities of the homologous unsubstituted saturated cyclic disulphides. Larger rings do not require any appreciable deviation from the normal value of the dihedral angle and therefore correspond more closely to the linear disulphides. This is substantiated from the spectrochemical investigations of CALVIN and co-workers (35) and the present author (see below). It is further strengthened by the calorimetric determinations of SUNNER (38).

In this investigation substituted cyclic disulphides have been studied and in particular carboxylic acid derivatives, which are specially suitable owing to their solubility properties. Although substituents stabilize the strained system a certain reactivity is found for the compounds derived from 1,2-dithiolane. A comparison of the properties of the homologous disulphide acids (IV), (I) and (V) and the observations made upon their preparation indicate that the dominating influence within the molecule of the disulphide group decreases distinctly with increasing ring size.

The significant properties of different types of disulphides have been correlated to each other and a common basis obtained from which conclusions can be drawn, thereby extending our knowledge about the cyclic disulphide systems. In order to make the examination more complete the spectrochemical studies include even the isomeric dithio-dibensoic acids and their dimethyl esters (10).

Finally it should be mentioned that photolysis experiments on 1,2-dithiolane have been performed by CALVIN and co-workers (35, 36). Recent work with monochromatic radiation (36) has shown that the number of photons required to break the S–S bond is of the order of unity, which makes reasonable the assumption of a repulsive excited state from which energy may be efficiently transferred. The present author has examined briefly the photolysis of *racem*-1,2-dithiolane-3,5-dicarboxylic acid (11) and of 1,2-dithiolane-4-carboxylic acid. The results imply opening of the rings by S–S bond fission, very likely with a homolytic splitting of the linkage into a biradical, which immediately reacts in some way. No quantitative examinations of the reaction mixtures have been made as yet. According to CALVIN and WHITNEY (36) the biradicals react with the solvent (alcohol).

Ultraviolet absorption

Ultraviolet absorption measurements mainly on aliphatic dialkyl disulphides have previously been reported by e.g. KOCH (72), BAER and CARMACK (73) and by BRANDT,

EMELÉUS and HASZELDINE (74). It is known that non-cyclic disulphides show one characteristic selective absorption in the vacuum ultraviolet region with a maximum at about 200 mμ and one absorption peak near 250 mμ in the near ultraviolet region. This characteristic 250 mμ maximum seems due to the excitation of the non-bonding p-electrons or the πp electrons if we consider the existing overlap of the unshared electron pairs. The present author has recently examined the spectra of some cyclic disulphides (11), and in order to interprete the possible influence of substituents the study was extended to include carboxylic substituted aliphatic disulphides. It was found that dithio-diacetic acid (dithio-diglycolic acid) has only continuous absorption in the wavelength region under question (220–330 mμ) with increasing extinction towards shorter wavelengths. An analogous spectral behaviour is reported by KOCH for di-*tert.* butyl disulphide (72). A carboxylic group thus causes the same effect as the three methyl groups attached to the same carbon atom. As these groups have different modes of inductive electronic effects it was considered likely that the shifts or complete changes were due to steric effects. KOCH had offered such an explanation for the anomalous behaviour of di-*tert.* butyl disulphide. It was, however, stated that an examination of the corresponding diselenides should be valuable for comparison. The selenium atoms are larger than the sulphur atoms (covalent radius : 1.17 Å and 1.04 Å resp. (75)) and substituents attached to the Se–Se group are thus more distant from each other than if they were linked to an S–S group. The spatial interactions of the substituents in a diselenide must therefore be smaller than in a disulphide and it should be possible to study pure electronic effects. An examination of the ultraviolet absorption spectra of some linear diselenides has now been published by BERGSON (76), from which it may be concluded that the diselenides are more suitable for theoretical studies than the disulphides, as their absorption is found at longer wavelengths and the two absorption bands are more separate. The discussion given in reference (11) may now be somewhat modified but also made more precise after comparison with the corresponding diselenide spectra and extension of the disulphide material. From the spectral behaviour of di-*tert.* butyl diselenide (76) BERGSON is able to give an account also for the continuous absorption of the corresponding disulphide. For, if the characteristic absorption band undergoes a hypsochromic shift of the same order of magnitude as that of the diselenide the two absorption bands of di-*tert.* butyl disulphide should be so close together that the resulting absorption would be continuous in the wavelength region examined. The continuous shift of the specific absorption for diselenides and disulphides with different number of C–H bonds (3, 2, 1, 0 resp.) towards shorter wavelengths may be accounted for by assuming hyperconjugation of the C–H σ-orbitals with the orbitals of the selenium or sulphur atom; a recent investigation of the infrared absorption (the C–Se bond) has substantiated this interpretation (77).

The examination of the dicarboxylic substituted disulphides clearly illustrate the different influence of substituents. The substances can be collected in two series as

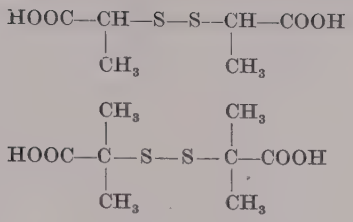
$$HOOC—CH_2—S—S—CH_2—COOH \quad (a)$$

$$HOOC—CH_2—CH_2—S—S—CH_2—CH_2—COOH \quad (b)$$

$$HOOC—CH_2—CH_2—CH_2—S—S—CH_2—CH_2—CH_2—COOH \quad (c)$$

and

$$HOOC—CH_2—S—S—CH_2—COOH \quad (a)$$



(d)

(e)

The different types of absorption are given in Table 4.

The spectra of dithio-diacetic acid (a), dithio-α,α′-dipropionic acid (d) and dithio-α,α′-di-*iso*-butyric acid (e) are shown in Fig. 1. The absorption curves for the diastereomers of (d) are nearly identical (11).

From the series (a)–(c) it can be seen that a carboxylic group in the γ-position of the sulphur atoms does not exhibit any influence on the characteristics of the disulphide group. The spectral behaviour of dithio-diacetic acid was discussed in reference (11). This work had indicated that there might be a change in the dihedral angle. The dihedral angle is principally determined by the repulsion of the non-bonding p-electrons and with changed electronic conditions of the disulphide group there should be a small change of the angle. BERGSON has, however, shown that considerable spectral differences occur for diselenides, even when the dihedral angles do not show much variation (76). Although no value of the dihedral angle of any carboxylic substituted disulphide is known, it seems justified to assume analogous behaviour for diselenides and disulphides. The continuous type of ultraviolet absorption for dithio-diacetic acid may therefore be explained by the combined results of a bathochromic shift of the absorption band in the vacuum ultraviolet region (in analogy to diselenium-diacetic acid (76);) and a hypsochromic shift of the usual 250 mμ absorption. The effect on the band in the near ultraviolet region is due to the inductive effect of the carboxylic groups, which involves the withdrawal of electrons from the disulphide group. The decrease in mutual repulsion of the electrons causes excitation at higher energy, thus a shift towards shorter wavelengths. An overlap of the two absorption bands gives the continuous spectrum. It can now be pointed out that a comparison of the disulphides (a)–(c) illustrates the influence of the carboxylic group on the disulphide system under analogous hyperconjugative conditions, whereas the series (a), (d), (e) shows the results of hyperconjugation and alkyl inductive effects with unchanged substitution for the carboxylic groups.

Table 4. UV absorption of some disulphide dicarboxylic acids and their salts (220–330 mμ) (solvent: alcohol and water resp.).

Substance	Type of absorption	
	Acid	Di-Na-salt
(a)	continuous	continuous
(b)	max. 245 mμ; min. 235 mμ	max. 246 mμ; min. 237 mμ
(c)	max. 249 mμ; min. 230 mμ	max. 245 mμ; min. 232 mμ
(d)	continuous	continuous
(e)	continuous	continuous

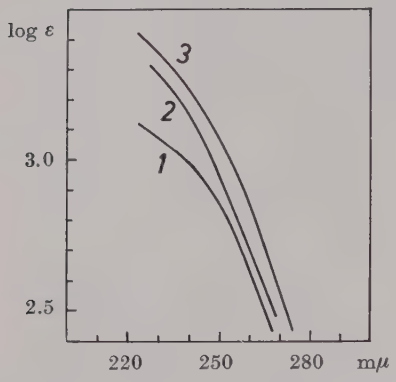


Fig. 1. UV absorption spectra of: (1) dithiodiacetic acid; (2) dithio-α,α′-dipropionic acid (racemic form); (3) dithio-α,α′-di-*iso*-butyric acid. Solvent: alcohol.

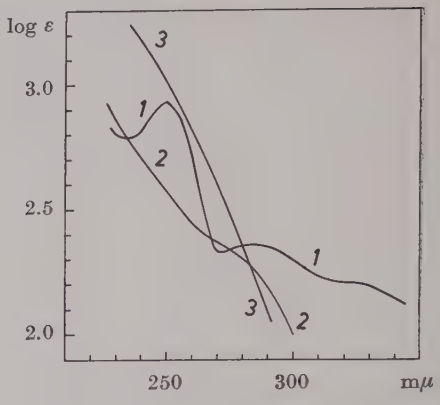


Fig. 2. UV absorption spectra of: (1) *racem*-1,2-dithiolane-3,5-dicarboxylic acid; (2) *racem*-1,2-dithiane-3,6-dicarboxylic acid; (3) *racem*-1,2-dithiepane-3,7-dicarboxylic acid. Solvent: alcohol.

The interpretation given above as to the relationship between the spectral behaviour of disulphides and the substituent influence on the S–S group should also apply for the cyclic derivatives examined in references (11) and (9). The investigation has now been extended to include also *racem*-1,2-dithiepane-3,7-dicarboxylic acid (V) and 1,2-dithiolane-4-carboxylic acid (VI) (and their salts). Fig. 2 shows the UV absorption of the racemic cyclic five-, six- and seven-membered disulphide-α,α′-

Table 5. UV absorption of some cyclic disulphide acids and their salts (220–360 mμ) (solvent: alcohol and water resp.).

Substance	Type of absorption	
	Acid	Na-salt (neutral)
1,2-Dithiolane-4-carboxylic acid	max. 330 mμ; min. 280 mμ	max. 330 mμ; min. 280 mμ
Rac.-1,2-Dithiolane-3,5-dicarboxylic acid	max. 250 mμ; min. 235 mμ (max. 285 mμ; min. 270 mμ; inflex. 330 mμ)	max. 330 mμ; inflex. 280 mμ; min. 300 mμ*
Rac.-1,2-Dithiane-3,6-dicarboxylic acid	inflex. *c.* 280 mμ	inflex. *c.* 275 mμ
Meso-1,2-Dithiane-3,6-dicarboxylic acid	continuous	inflex. *c.* 273 mμ
Rac.-1,2-Dithiepane-3,7-dicarboxylic acid	continuous	continuous
Meso-1,2-Dithiepane-3,7-dicarboxylic acid	continuous	continuous

* The acid Na-salt has: inflex. *c.* 246 *mμ*; min. 270 *mμ*; max. 280 mμ; min. 300 mμ; max. c. 320 mμ.

Table 6. UV absorption of some 4-substituted 1,2-dithiolanes (220–380 mμ) (solvent: alcohol).

Substance	Type of absorption
1,2-Dithiolane-4-carboxylic acid	max. 330 mμ; min. 280 mμ
4,4-Dimethyl-1,2-dithiolane	max. 331 mμ; min. 284 mμ
4,4-Bis-hydroxymethyl-1,2-dithiolane	max. 328 mμ; min. 285 mμ; inflex. 255 mμ
1,2-Dithiolane-4-semicarbazone	max. 330 mμ, min. 302 mμ; max. 236 mμ
2,3-Dithia-(4,5)-spirodecane	max. 329 mμ; min. 283 mμ; inflex. *c.* 260 mμ
2,3,7,8-Tetrathia-(4,4)-spirononane	max. 333 mμ; min. 287 mμ
2,6,7-Trithia-(3,4)-spirooctane	max. 354 mμ; min. 303 mμ; max. 264 mμ; min. 257 mμ

dicarboxylic acids. The spectral properties of *meso*-(V) are given in reference (11). The different types of absorption of the cyclic disulphides investigated are collected in Tables 5 and 6.

The ultraviolet absorption spectra of 1,2-dithiolane-4-carboxylic acid (VI) and 2,3,7,8-tetrathia-(4,4)-spirononane (VIII) are illustrated in Fig. 3. 1,2-Dithiolane-3-carboxylic acid has an absorption peak at 280 mμ (62).

It should be observed that the absorption curves of the five- and six-membered saturated cyclic disulphides have been recorded by CALVIN and co-workers (35) together with that of 4-thioctic acid (4,8-dithio-*n*-octanoic acid), representing the seven-membered ring system. A displacement of the absorption top to longer wavelengths is observed, when the size of the disulphide ring diminishes. This can be interpreted as due to the changed electronic conditions around the S–S group. Thus the cis position of the disulphide group in 1,2-dithiolane derivatives involves a compression of the *p*-electron orbitals, which results in an increased repulsion between the two non-bonding *p*-electron pairs and hence excitation by less energy. It appears from references (9) and (11) and from Tables 5 and 6 that the influence of the substituents resembles that of the linear disulphides. Special attention is drawn to the interesting fact that the spectral behaviour of 1,2-dithiolane itself and the 4-substituted derivatives are closely related.

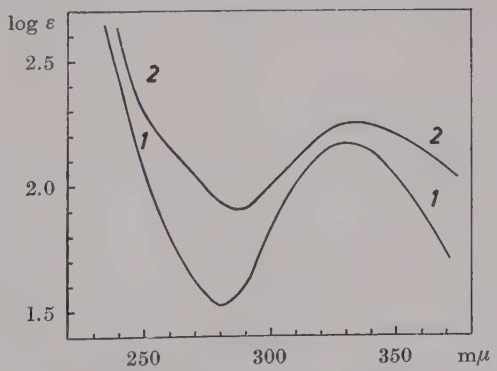


Fig. 3. UV absorption spectra of: (1) 1,2-dithiolane-4-carboxylic acid; (2) 2,3,7,8-tetrathia-(4,4)-spirononane. Solvent: alcohol.

The ultraviolet absorption curve of *racem*-1,2-dithiolane-3,5-dicarboxylic acid (IV) is interesting since in addition to the 250 mμ peak it also contains two absorption bands of lower intensity at longer wavelengths. It seems difficult to give an explanation for this observation.

It is most interesting to note the appreciable change in UV absorption of *racem*-(IV) upon neutralization of the acid (11). As no analogous effects have been found by the present author for 1,2-dithiolane-4-carboxylic acid and 6-thioctic acid (the spectra for the acid and salt are similar), it seems justified to ascribe the observed change to the substitution of carboxylic groups at the α-position to the disulphide group. However, a detailed interpretation cannot be given at present.

The spectrochemical investigation has been extended to include also the study of isomeric dithio-dibensoic acids and their dimethyl esters (10). The ways of approaching the problem are certainly somewhat different for the aromatic derivatives on one side and the non-aromatic on the other, but by this examination the effect of conjugation of the disulphide group is clearly demonstrated. The *m*-compounds show less intense absorption than the *o*- and *p*-isomers. Displacements towards longer wavelengths are observed for the latter isomers. A recent paper by KISS and MUTH (78) describes the UV absorption spectrum of *o,o'*-dithio-dibensoic acid in addition to those of the related sulphide, selenide and diselenide. Our experimental results seem consistent.

Infrared absorption

The applications of infrared research to organic sulphur compounds have hitherto been rather few and so this investigation has in view not only a comparison of the homologous linear and cyclic disulphide dicarboxylic acids and different 1,2-dithiolane derivatives but also the provision of further material for qualitative deductions as to the properties of the S–S group. It is certainly true that the sulphur–sulphur bond is best studied using Raman spectroscopy but by careful analysis even the infrared absorption spectra recorded in the potassium bromide prism region may give valuable information (7, 9–11, 44). The disulphide stretching frequency is generally assigned the region 400–500 cm^{-1} (25.0–20.0 μ) (79) and the S–S peaks are in general regarded as ill-defined and difficult to characterize due to low intensities (small changes in the dipole moment upon stretching of the group). For the aromatic disulphides CYMERMAN and WILLIS (80) have reported the region 430–490 cm^{-1} (23.2–20.4 μ). The carbon–sulphur stretching frequency is assigned to 600–700 cm^{-1} (16.7–14.3 μ).

Interpretations of the absorption curves have not been possible for all the disulphides investigated but conclusions may often be drawn from a comparison of related substances, especially if one of the compounds shows a simple spectrum. A typical example is found for the diastereomers of dithio-α,α'-dipropionic acid (44), where the extreme simplicity of the spectrum of the racemic isomer allows assignments of the bands to be made for both the acids. In general, care should be exercised in interpretation and reservations entered in case of uncertainties. A considerable extension of the materials examined in reference (11) has now been made. The frequencies ascribed to the carbon–sulphur and sulphur–sulphur stretching vibrations for linear and cyclic disulphide dicarboxylic acids are collected in Tables 7 and 8 respectively. The wavelengths of the absorption bands for dithio-diacetic acid, dithio-β,β'-dipropionic acid and dithio-α,α'-di-*iso*-butyric acid within the potassium

Table 7. Frequencies ascribed to the C–S and S–S stretching vibrations for some linear disulphide dicarboxylic acids.

Substance	Wavelength, μ		Wavenumber, cm^{-1}	
	C–S	S–S	C–S	S–S
Dithio-diacetic acid	15.05	*c.* 21.8*	664	*c.* 459*
Rac.-Dithio-α,α′-dipropionic acid .	15.10	20.5	662	488
Meso-Dithio-α,α′-dipropionic acid .	14.82; 15.10	20.6	675; 662	485
Dithio-β,β′-dipropionic acid . . .	15.25 and (or) 15.60	19.0	656; 641	526
Dithio-α,α′-di-*iso*-butyric acid . .	15.50	19.65	645	509
Dithio-γ,γ′-di-*n*-butyric acid . . .	†	†	†	†

* Uncertainty involved. † No assignment possible.

Table 8. Frequencies ascribed to the C–S and S–S stretching vibrations for some cyclic disulphide dicarboxylic acids.

Substance	Wavelength, μ		Wavenumber, cm^{-1}	
	C–S	S–S	C–S	S–S
Rac.-1,2-dithiolane-3,5-dicarboxylic acid	15.06	18.57	664	539
Rac.-1,2-dithiane-3,6-dicarboxylic acid	15.10	20.70	662	483
Meso-1,2-dithiane-3,6-dicarboxylic acid	14.50 and 14.72	19.45*	690; 679	514*
Rac.-1,2-dithiepane-3,7-dicarboxylic acid	†	†	†	†
Meso-1,2-dithiepane-3,7-dicarboxylic acid	†	†	†	†

* Uncertainty involved. † No assignment possible.

Table 9. The infrared absorption of some linear dithio-dicarboxylic acids. (11–23 μ; KBr phase).

b = broad; vs = very strong; s = strong; m = medium; w = weak; sh = shoulder.

Dithio-diacetic acid			Dithio-β,β′-dipropionic acid			Dithio-α,α′-di-*iso*-butyric acid		
Wavelength in μ	Wavenumber in cm^{-1}	Character of the band	Wavelength in μ	Wavenumber in cm^{-1}	Character of the band	Wavelength in μ	Wavenumber in cm^{-1}	Character of the band
12.85	778	w	12.30	813	vs	12.40	806	vs
13.04	767	w	13.18	759	w	13.10	763	w
15.05	664	s	15.25	656	s	15.50	645	s
17.43	574	m	15.60	641	s	18.12	552	vs
17.71	565	m	18.15	551	m	18.5	541	sh
19.7	508	w b	19.0	526	m b	19.65	509	m
c. 21.8	*c.* 459	m b						

bromide prism region are given in Table 9. The frequencies ascribed to the stretching vibrations of the S–S group in some 1,2-dithiolane derivatives are reported in Table 2, reference (9).

Unfortunately no assignments were possible for the 1,2-dithiepane derivatives due to the complicated nature of the absorption curves. This seems due to the structural vibrations which are more pronounced with increasing number of methylene groups in the ring or the chain. In addition to the monomeric *racem-* and *meso-*1,2-dithiepane-3,7-dicarboxylic acid the polymer described in reference (4) has been investigated. The outlines of the curves are rather similar but distinct differences occur in the region 7–9 μ ("finger print region"), where the polymer has a set of sharp bands. In the potassium bromide prism region, where the carbon–sulphur and sulphur–sulphur bands usually occur, a certain similarity is found. The behaviour of the S–S group in larger rings should in reality resemble roughly that of well-defined polymers.

It seems possible to conclude from the above that the frequencies of the carbon–sulphur stretching vibrations for the disulphide acids vary within a rather close interval which is consistent with that postulated in general. It should be noted that the shift towards lower frequencies for dithio-α,α'-di-*iso*-butyric acid as compared with dithio-diacetic acid is in agreement with the results of SHEPPARD (81) that the C–S stretching frequency for *tert.* alkyl sulphides is appreciably lower than that of similar compounds with primary alkyl groups. These differences may be interpreted in terms of changes in the force constants of the linkages. Further support is thereby given to the above-mentioned hyperconjugation (cf. the discussion of UV spectra) of the C–H σ-orbitals with the orbitals of the sulphur atom. For the 4-substituted 1,2-dithiolanes and the aromatic disulphides no assignments as to the C–S linkages have been possible due to structural vibrations at frequencies in the vicinity of those expected for carbon–sulphur bonds.

This investigation has shown that the region, which is generally assigned to the disulphide stretching frequency (400–500 cm^{-1}), should be somewhat modified. In fact, the disulphide acids have their S–S absorption bands at frequencies near or higher than 500 cm^{-1}. As could be expected special properties have been found for the 1,2-dithiolane derivatives. The disulphide bands occur at higher frequencies

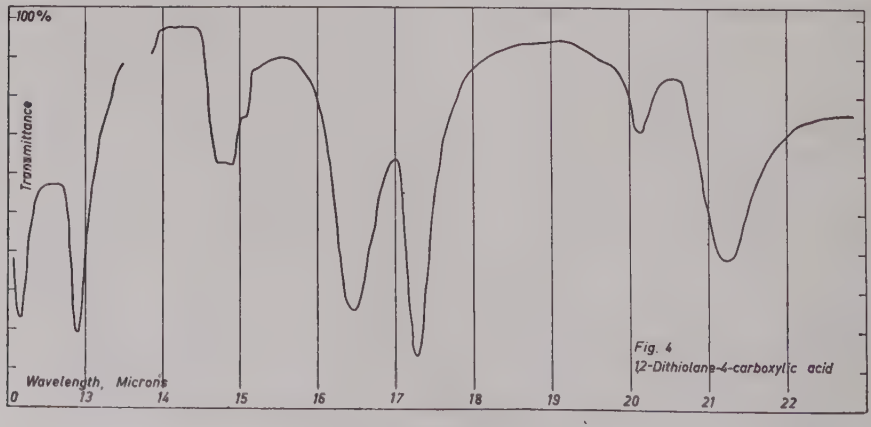


Fig. 4.

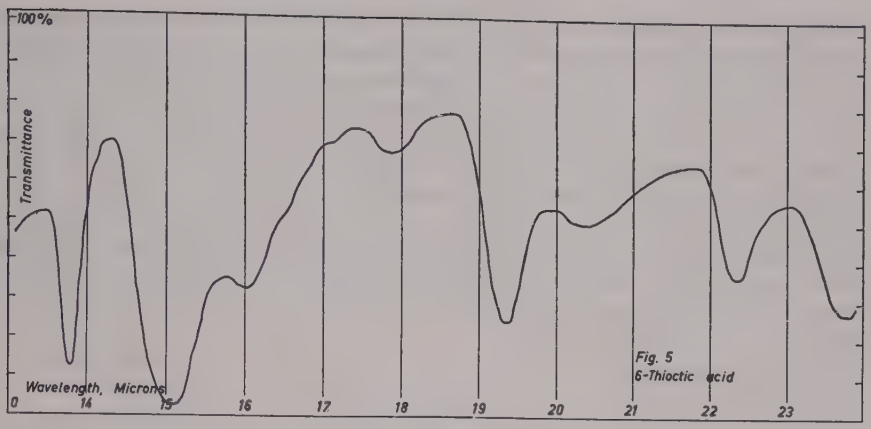


Fig. 5.

than those of other disulphides and this reflects well the electronic conditions around the S–S group in the five-membered ring. It should be noted that the 4-substituted 1,2-dithiolanes are in general characterized by higher S–S frequencies than the 3-substituted. However, variation occurs to some extent even for closely related compounds. As this investigation seems to be the first involving infrared studies on cyclic disulphides (the IR spectrum of 6-thioctic acid in the NaCl region has been reported (22)) with regard to the carbon–sulphur and sulphur–sulphur bonds, it may be justified to present the IR spectra of 1,2-dithiolane-4-carboxylic acid and 6-thioctic acid (Figs. 4 and 5) in the potassium bromide region, although no unambigous interpretation of the bands can be offered at present due to the rather complicated nature of the curves. This seems especially well-grounded, if we consider the possible biochemical importance of these substances.

For the aromatic disulphides the S–S stretching vibration frequencies have been found within or close to the region proposed (430–490 cm^{-1}). The reader is directed to Figs. 3 and 4 in reference (10) for detailed information.

Polarimetry

The enanthiomorphs of 1,2-dithiolane-3,5-dicarboxylic acid show a very high molecular rotation in different solvents (abs. ethanol, $[M]_D^{25} = +1092°$ and $-1088°$ resp.) (5). It should be noted that the rotation in aqueous medium depends on the acidity of the solution, which can be directly connected with the observed gradual change of the character of the ultraviolet absorption spectrum upon neutralization of the acid (11). The preliminary resolution experiments of *racem*-1,2-dithiepane-3,7-dicarboxylic acid also accounts for the high rotatory power. As maximum optical activity has not yet been obtained, further discussion must be postponed. It is, however, interesting to note that the specific rotation is higher than that of the corresponding 1,2-dithiane derivative (14). This observation may indicate an alternating effect within the homologous series or may be connected with the more symmetrical structure of the six-membered disulphide acid. The high rotatory power of cyclic disulphides has been somewhat discussed in reference (5). Attention is called to the racemization tendency of the enanthiomorphs of 1,2-dithiolane-3,5-dicarboxylic acid (5).

Very interesting polarimetric investigations of the redox process mercaptan–disulphide (82) and of the diselenide dismutations (83) have been made by FREDGA. The marked difference in activity of disulphide and mercaptan makes the use of polarimetry advantageous for the establishment of redox processes. The reaction between *racem*-1,2-dithiolane-3,5-dicarboxylic acid (IV) and the related dimercaptan has been preliminarily studied. The kinetic interpretation of the results must, however, wait until further experiments are made.

It may finally be pointed out that no reaction between the cyclic five-membered disulphide acid (IV) and dithio-diacetic acid could be obtained under conditions, in which the corresponding reaction occurs for diselenides. The difference in reactivity in this respect between the Se–Se and S–S groups (83) thus seems to include even the strained 1,2-dithiolane system.

Polarography

In an attempt to find a method of comparing the ring stability of the cyclic disulphide acids having different ring sizes a polarographic investigation has recently been undertaken in collaboration with Dr. B. NYGÅRD (84). A brief note that the

Table 10. Half-wave potentials vs. S.C.E. at pH = 2.2 (citrate buffer) for some cyclic disulphide acids (conc. = 1.00×10^{-3} *M*).

Substance	Half-wave potential, volt
Rac.-1,2-Dithiolane-3,5-dicarboxylic acid	−0.33*
Rac.-1,2-Dithiane-3,6-dicarboxylic acid	−0.76
Meso-1,2-Dithiane-3,6-dicarboxylic acid	−0.75
Rac.-1,2-Dithiepane-3,7-dicarboxylic acid	−0.92
Meso-1,2-Dithiepane-3,7-dicarboxylic acid	−0.93
6-Thioctic acid	−0.36
1,2-Dithiolane-3-carboxylic acid	−0.37
1,2-Dithiolane-4-carboxylic acid	−0.37

* A bad wave in acetate buffer, pH = 4.6: — 0.44 V.

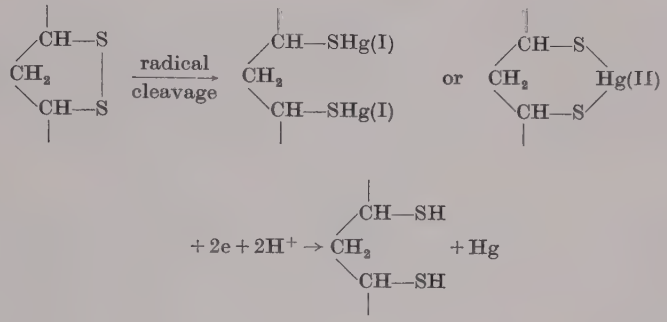
Table 11. Half-wave potentials vs. S.C.E. in different standard buffer solutions for some 4-substituted 1,2-dithiolanes (conc. 1.00×10^{-3} *M*).

Substance	Half-wave potential, volt			
	Citrate buffer pH = 2.2	Acetate buffer pH = 4.6	Phosphate buffer pH = 7.0	Borate buffer pH = 9.2
1,2-Dithiolane-4-carboxylic acid	−0.37	—	−0.65*	−0.76*
4,4-Bis-hydroxymethyl-1,2-dithiolane	−0.31	−0.44	−0.68	−0.70
4,4-Dimethyl-1,2-dithiolane	−0.34	—	−0.68	−0.78
2,3-Dithia-(4,5)-spirodecane	−0.34	−0.49	−0.64	−0.79
2,6,7-Trithia-(3,4)-spirooctane	−0.33	−0.48	−0.62	−0.77
2,3,7,8-Tetrathia-(4,4)-spirononane	−0.40	−0.55	−0.68	−0.83

* The wave is somewhat deformed.

disulphide linkage in 6-thioctic acid is reducible at the dropping mercury electrode (21) seems to be the only report in the literature about the polarographic behaviour of cyclic disulphides. A number of substances have been examined and the half-wave potentials vs. the saturated calomel electrode (S.C.E.) are collected in Tables 10 and 11.

At pH = 2.2 all the 1,2-dithiolane derivatives give very good waves which are reversible in character. The wave heights and the relations log $[i/(i_d - i)]$ vs. the applied potentials E indicate a two-electron reduction. Analogous to the polarographic behaviour of some aliphatic disulphides (cystine, glutathione) the waves obtained seem to be due to the reduction of Hg complexes which are formed on the drop at the rupture of the S–S linkage. The electroreduction should thus proceed according to, e.g.



The six- and seven-membered cyclic disulphide dicarboxylic acids give polarographic waves only in acid solution and the waves are rather drawn out indicating irreversible electroreduction. In both the cases the irreversibility is more pronounced for the meso acids than for the racemic isomers.

The fact that the polarographic effect seems based upon the intermediate Hg complex formation makes a direct comparison inadequate for the establishment of a possible difference in ring stability. On the other hand, a study of the outlines of the curves may indicate roughly the degree of irreversibility which is connected with the primary reaction, i.e. with the homolytic cleavage of the S–S bond. It can thus be concluded that *racem*-1,2-dithiolane-3,5-dicarboxylic acid reacts more readily than the homologous acids with larger rings. In fact, the waves of the 1,2-dithiepane derivatives resemble those obtained for dithio-diacetic acid (irreversible in character) (85). The polarographic data are thus in agreement with the above results.

It is obvious from the foregoing that the polarographic effects of the 1,2-dithiolane derivatives are of special interest. It should be noted that 4-substituted 1,2-dithiolanes give in general good waves over the whole pH range. Only the carboxylic substituted derivative shows slight deformations at higher pH. On the other hand, it can be seen from Fig. 6 that in neutral medium the wave of *racem*-1,2-dithiolane-3,5-dicarboxylic acid is quite deformed and at higher pH no waves are found. This observation should probably be connected with the above discussed effect of anions on the characteristic UV absorption spectrum and as 6-thioctic acid has been found to give polarographic waves similar to those of the 4-substituted 1,2-dithiolanes, it seems justified to postulate a considerable effect of a carboxylic group only if it is substituted at the carbon atom in α-position to the S–S group. This establishment

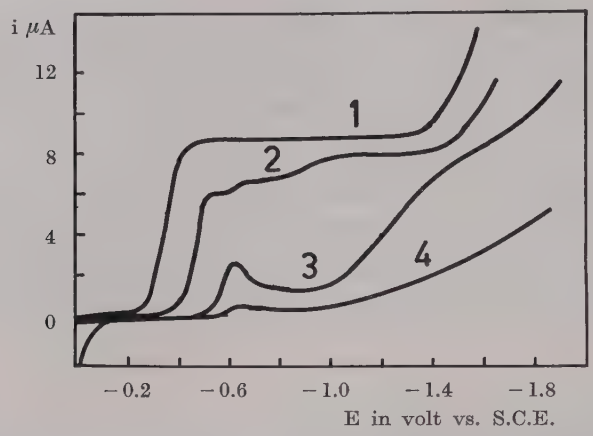


Fig. 6. Polarograms of 1.00×10^{-3} *M racem*-1,2-dithiolane-3,5-dicarboxylic acid in various buffers: (1) citrate buffer, pH = 2.2; (2) acetate buffer, pH = 4.6; (3) phosphate buffer, pH = 7.0; (4) borate buffer, pH = 9.2. (The solutions contain 0,005 % gelatin as max.-suppressor and 0,1 *M* KNO_3.)

is supported by the behaviour of 1,2-dithiolane-3-carboxylic acid. The salt of the five-membered cyclic disulphide dicarboxylic acid is in some way stabilized against the attack by mercury. It is difficult to understand the real significance of this observation, but there seems to exist a correlation between this behaviour and the spectral properties.

It should finally be noted that diselenides are characterized by reversible effects over the whole pH range. Diseleno-diacetic acid has been studied in detail by NYGÅRD (86). The formation of electroreducible Hg complexes on the mercury drop is more easily realized for selenium compounds. Such a difference in reactivity with mercury has already been established by FREDGA for the aliphatic S–S and Se–Se groups (87, 88). In this respect the 1,2-dithiolane derivatives resemble the diselenides and show greater affinity to mercury than disulphides in general except those involving heterocyclic structures (89).

Steric relations

If the optically active 1,2-dithiolane-3,5-dicarboxylic acid (IV) can be sterically related to the glyceric aldehyde system, a method is offered for the establishment of the absolute configuration of 6-thioctic acid. It therefore seemed important to establish the configuration of (IV).

In the problem of determining the configurative relationships between optically active substances the formation of quasi-racemic compounds plays an important role. A molecular compound formed from two optically active substances is considered as a quasi-racemic compound if each component forms a molecular compound only with one antipode of the other. It is then obvious that the steric factors are of primary importance in the formation of the compounds. The quasi-racemate method has been thoroughly investigated and successfully applied to a number of steric problems by FREDGA and collaborators (90, 91). Although X-ray diagrams often prove to be of value (92), the existence of the quasi-racemic compounds is

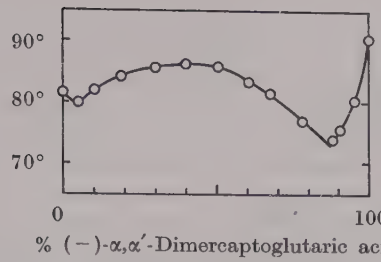


Fig. 7. Melting point diagram for the system (+)-α,α′-dimethylglutaric acid and (−)-α,α′-dimercaptoglutaric acid.

usually demonstrated by means of melting point curves. A further method, involving the use of infrared absorption measurements to determine the existence of quasi-racemates has recently been presented by ROSENBERG and SCHOTTE (43).

It is difficult to find a substance with established absolute configuration for direct comparison to the enanthiomorphs of (IV). However, reduction of the disulphide acids give optically active α,α′-dimercaptoglutaric acids (IX) (the product has opposite mode of rotation) in reactions which do not affect the centres of asymmetry (5). These mercapto acids show a pronounced tendency for racemate formation, and as preliminary work on the melting point diagram of the enanthiomorphs indicated similarity to the curve given by FREDGA (93) for the antipodes of α,α′-dimethylglutaric acid (X), it seemed justified to try to correlate α,α′-dimercaptoglutaric acid and the dimethyl compound by the quasi-racemate method. Optically active α,α′-dimethylglutaric acid (X) has been connected to the glyceric aldehyde system by FREDGA (94). However, a complete thermal analysis of the phase diagrams should be avoided, since it has been found that the melting point of the mercapto acid depends upon the rate of heating due to partial decomposition. The method of instantaneous melting (95) was applied but nevertheless reproducible results could only be obtained for the system (+)-(X) and (−)-(IX), where the

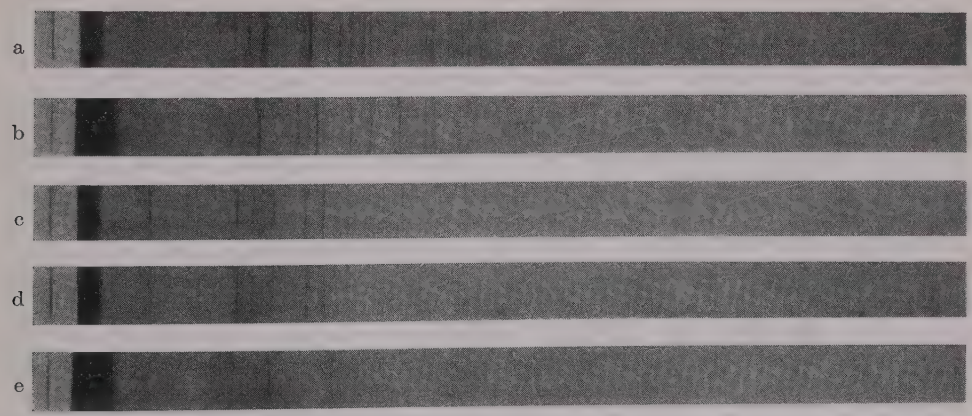
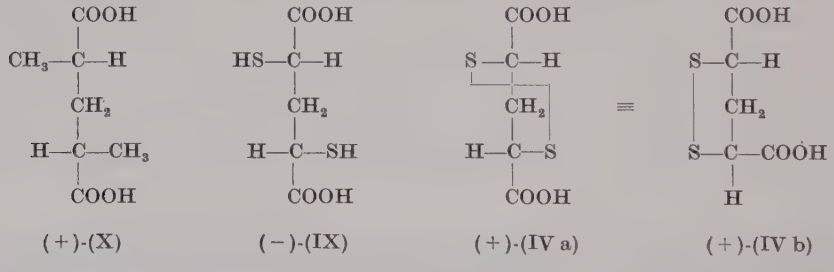
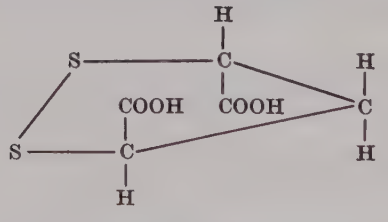


Fig. 8. Guinier powder photographs (Cu-Kα radiation) of: (a) *racem*-α,α′-dimercaptoglutaric acid; (b) (+)-α,α′-dimercaptoglutaric acid; (c) (+)-α,α′-dimethylglutaric acid; (d) equimolar amounts of (+)-α,α′-dimethylglutaric acid and (−)-α,α′-dimercaptoglutaric acid; (e) equimolar amounts of (+)-α,α′-dimethylglutaric acid and (+)-α,α′-dimercaptoglutaric acid.

melting points were in general lower than those of the systems (+)- and (−)-(IX), and (+)-(X) and (+)-(IX). The approximate outlines of the two latter diagrams resembled each other and suggested molecular compounds in the ratio 1:1 melting 40°–50° higher than the optically active components. However, as the curves were quantitatively unreliable they are omitted here. Fig. 7 shows the remaining diagram, (+)-(X) and (−)-(IX), which seems to consist of a solid solution between 0 % and about 85 % of (IX) with a minimum at about 5 % and a maximum at about 50 %. The rest of the curve is of the eutectic type. This interpretation has been confirmed by studies of contact preparations (96) and by means of X-ray powder photographs (see Fig. 8, *c* and *d*). It may be mentioned that a melting point curve of the same type is described by PETTERSSON (97) for the system (+)-α-phenylhydrocinnamic acid and (+)-α-(2-thienyl)-hydrocinnamic acid. The above results indicate the connection between direction of rotation and configuration but it should be stressed that in this case definite conclusions must not be drawn from melting point curves only. The systems have therefore been investigated with X-rays. The different powder photographs are shown in Fig. 8. The true racemic character of *racem*-(IX) is obvious from comparisons of *a* and *b*. If we compare *c* with *d* and *e*, there is a close similarity between *c* and *d*, whereas differences in line distributions occur for *d* and *e*. This is consistent with the existence of a quasi-racemic compound between equivalent amounts of (+)-(X) and (+)-(IX). Infrared absorption studies support this view.

On the basis of the results obtained it seems possible to relate (X) to the sulphur compounds (IX) and (IV) by the following stereo-formulae:





(IV c)

The formulae (IV a) and (IV b) are perspectively reproduced in (IV c).

There are several cases known where quasi-racemic compounds can be formed between components which are structurally identical except for the replacement of a CH_2 group in the one by an S atom in the other (98). However, the replacement of the S–S group in linear disulphides by CH_2–CH_2 involves a considerable structural change due to the skew configuration of disulphides and the changed bond lengths. The differences are obviously large enough to prevent the formation of a quasi-

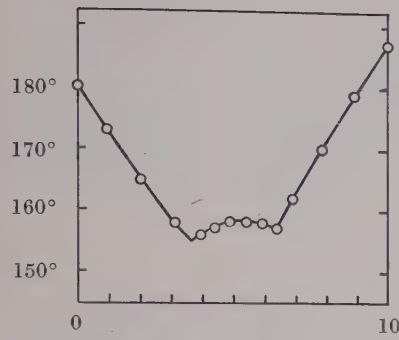


Fig. 9. Melting point diagram for the system (+)-thiophane-2,5-dicarboxylic acid and (−)-1,2-dithiolane-3,5-dicarboxylic acid.

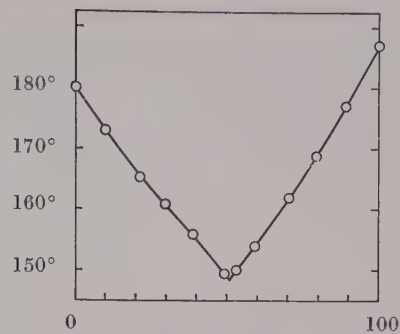
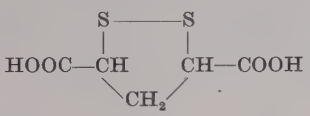
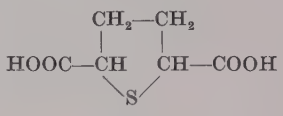


Fig. 10. Melting point diagram for the system (+)-thiophane-2,5-dicarboxylic acid and (+)-1,2-dithiolane-3,5-dicarboxylic acid.

racemate. This has been established by HEDLUND in the case of the system dithio-α,α′-dipropionic acid and α,α′-dimethyladipic acid (99). The present investigation has shown that of the factors controling the above-mentioned structural change, the configuration of the S–S group is by far the most important. This can be seen from Figs. 9 and 10, where the melting point curves of the systems (−)-1,2-dithiolane-3,5-dicarboxylic acid (IV), (+)-thiophane-2,5-dicarboxylic acid (XI) and (+)-(IV), (+)-(XI) respectively are given. The diagram for the enanthiomorphs of (IV) is reported in reference (5) and that of the antipodes of (XI) in reference (12).



(IV)



(XI)

(XI) may be considered as formally derived from (IV) by the replacement of an S–S group by CH_2–CH_2 and a CH_2 by an S atom. As the acids with the same mode of rotation give a curve of eutectic type (Fig. 10) and those of opposite rotation form a molecular compound in the ratio 1:1, we may conclude that the acids with the *same direction of rotation* have the "same configuration". Furthermore the probable existence of a quasi-racemic compound between (−)-(IV) and (+)-(XI) is indicated by infrared absorption measurements. The spectrum of the mixture of equivalent amounts of (−)-(IV) and (+)-(XI) within the sodium prism region resembles closely that of *racem*-(IV) (11). Fig. 11 represents part of the infrared spectra of both the equimolar mixtures (+), (−) and (+), (+), recorded between 6.5 μ and 9.0 μ, where pronounced differences occur.

This result illustrates well the consequence of the *cis*-configuration (dihedral angle probably near 0°) of the disulphide group in 1,2-dithiolane derivatives with their nearly planar ring structure.

In some cases information about the steric relations between similarly constituted compounds may be obtained by measuring the optical activity in a number of

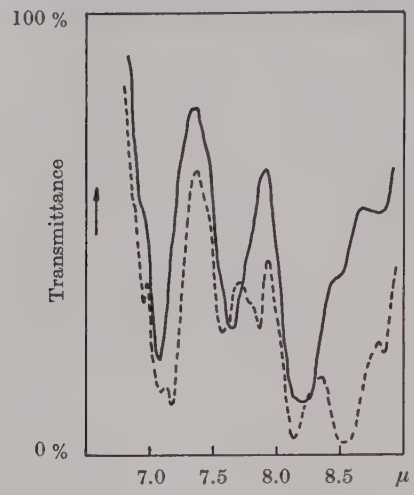


Fig. 11. IR absorption spectra (6.5–9.0 μ) of equimolar amounts of: (+)-thiophane-2,5-dicarboxylic acid and (−)-1,2-dithiolane-3,5-dicarboxylic acid; (+)-thiophane-2,5-dicarboxylic acid and (+)-1,2-dithiolane-3,5-dicarboxylic acid (dotted curve).

Table 12. The molecular rotation, $[M]_D^{25}$, in different solvents for (−)-α,α′-dimercaptoglutaric acid and (−)-α,α′-dimercaptoadipic acid.

Solvent	Molecular rotation	
	(−)-α,α′-Dimercaptoglutaric acid (Ref. (5))	(−)-α,α′-Dimercaptoadipic acid (Ref. (14))
Water (both carboxylic groups neutralized)	− 60°	− 39°
Glacial acetic acid	−115°	−147.5°
Ethanol (abs.)	−143°	−126°
Ethyl acetate	−162°	−147.5°

Table 13. The molecular rotation, $[M]_D^{25}$, in different solvents for (+)-1,2-dithiolane-3,5-dicarboxylic and (−)-1,2-dithiane-3,6-dicarboxylic acid.

Solvent	Molecular rotation	
	(+)-1,2-Dithiolane-3,5-dicarboxylic acid	(−)-1,2-Dithiane-3,6-dicarboxylic acid
Water (neutral salt)	+ 688°	−699°
Ethanol (abs.)	+1092°	−405.5°
Ethyl acetate	+1095°	−354.5°
Hydrochloric acid (dil.)	+1407°*	+263°†
Glacial acetic acid	+1470°	− 95°

* 2*N* HCl. † 0.4*N* HCl.

different solvents (100). Compounds with the same absolute configuration should than show the same mode of variation of the optical activity. The adipic and glutaric acid derivatives are compared in Tables 12 and 13 with respect to the mercaptans and disulphides. A certain similarity is found for the disulphides but due to the difference in dihedral angle of the S–S groups in the five- and six-membered cyclic compounds it is possible that the structural differences are too large to allow any conclusions from the activity data.

Structure of some polysulphides

As the formation of monosulphides in the above mentioned syntheses of cyclic disulphides from dibromo acids and alkali disulphides might be connected with the existence of an unstable intermediate with coordinatedly linked sulphur, it seemed justified to somewhat consider the structure of some polysulphides. This investigation (7) was performed on tri- and tetrasulphides of spirane structures (54–56) which is especially well-grounded as the related disulphides are 1,2-dithiolane derivatives (9). The results, which indicate unbranched sulphur chains, are given in reference (7). In addition to the further references given there, it may be mentioned that analogous conclusions have recently been drawn by means of tracer technique (101), with X-ray analyses (102) and Raman spectroscopy (103) as regards the structure of some other organic di- and polysulphides.

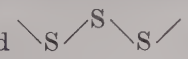
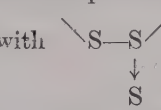
Additional support to the structures postulated for the polysulphides examined in reference (7) has now been obtained by polarographic studies. The compounds give well-defined polarographic waves at half-wave potentials (vs. S.C.E.), which are close to those given for the 1,2-dithiolane derivatives in Table 11. The heights of the waves are about 50 % greater than for the disulphides, and the polarographic behaviour suggests a structure with three similar sulphur atoms, which is consistent with the postulated  but not with  . A structure of the latter type must give rise to more than one polarographic wave. The half-wave potentials are given in Table 14.

Table 14. Half-wave potentials vs. S.C.E. of two polysulphides in different buffers (conc. 1.00×10^{-3} *M*).

Substance	Half-wave potential, volt		
	Citrate buffer pH = 2.2	Phosphate buffer pH = 7.0	Borate buffer pH = 9.2
2,6,7,8-Tetrathia-(3,5)-spirononane	− 0.39	− 0.67	− 0.77
5,5-Dimethyl-1,2,3-trithiane	− 0.40	− 0.68	− 0.78

Experimental

For further details about the techniques of the *ultraviolet* and *infrared absorption measurements* and the *polarographic work* the reader is referred to references (7), (9–11) and (84).

The preparations for the *melting point diagrams* were made by dissolving exactly weighed amounts of the components in acetone of high purity. The solvent was evaporated at room temperature and the residue removed *in vacuo* after powdering. The melting points were determined in capillary tubes with preheated apparatus or rapid heating (calibrated thermometer; electrically heated apparatus except for the determinations with instantaneous melting, when a sulphuric acid bath (of the usual type) was used).

X-ray powder photographs were taken in a focusing camera of the GUINIER (104) type with Cu-K_α radiation. The time of exposure was three hours. The preparations were obtained as above.

Dithio-α,α′-di-iso-butyric acid.—The substance was recrystallized from water (105). M.p. 198°.

Anal. Subst., 65.48 mg: 7.88 ml of 0.0696*N* NaOH. Equ. wt. Calc. 119.2; Found 119.4.

1,2-Dithiolane-4-carboxylic acid.—The method of preparation is outlined above. The details will be given in reference (58). The acid was recrystallized from benzene-cyclohexane. M.p. 76.5°–77.5°.

Anal. Subst., 33.20 mg: CO_2, 38.89 mg; H_2O, 11.61 mg.
„ , 18.25 mg: 6.86 ml of 0.0709*N* NaOH.
„ , 78.41 mg: 7.32 ml of 0.0709*N* NaOH.
$C_4H_6O_2S_2$ (150.22) Calc. C 31.98; H 4.03; S 42.68; Equ. wt. 150.2; Mol. wt. 150.
Found C 31.96; H 3.92; S 42.72; Equ. wt. 151.1; Mol. wt. 146.

The molecular weight has been determined by the ebullioscopic method with acetone as a solvent (cf. 9).

The related dimercaptan was obtained by reduction of the disulphide with zinc in ammoniacal solution. M.p. 57°–60°. (Cf. also (106)).

Anal. Subst., 36.97 mg: 4.89 ml of 0.0999 *N* J_2. Equ. wt. Calc. 76.1; Found 75.7.

Summary

Racem-1,2-dithiolane-3,5-dicarboxylic acid, the enanthiomorphs of 1,2-dithiepane-3,7-dicarboxylic acid and some related compounds have been prepared.

The synthesis, separation into diastereomers and configuration of the starting materials, α,α′-dibromoglutaric and -pimelic acid, have been discussed.

A survey of methods for the preparation of α,α′-dimercapto-dicarboxylic acids is given. The possible modes of reaction in the preparation of cyclic disulphides from halogenides and alkali disulphide are pointed out.

1,2-Dithiolane-4-carboxylic acid, possibly the disulphide present in asparagus, has been prepared.

Special attention has been paid to the study of the properties of cyclic disulphides with different ring sizes by physico-chemical methods.

The influence of substituents like the carboxylic group on the characteristic UV spectrum of disulphides has been interpreted as due to inductive effects. 3- and 4-Substituted 1,2-dithiolanes have been examined; a close similarity between 1,2-dithiolane itself and the 4-substituted derivatives is established.

Infrared absorption studies of the C–S, S–S, and C=S linkages are presented. Higher frequencies than those in general accepted for disulphides have been ascribed to the S–S stretching vibrations in the 1,2-dithiolane derivatives. The infrared absorption behaviour of the carbonyl groups in acid salts has been briefly treated.

Polarographic studies have been made on the five-, six- and seven-membered cyclic disulphide acids. The 1,2-dithiolane derivatives (including 6-thioctic acid) give good polarographic waves which resemble those of linear diselenides. The influence of the substituents on the mercury attack of the S–S linkage at different pH is indicated for the 1,2-dithiolanes.

The steric relationship between 1,2-dithiolane-3,5-dicarboxylic acid and α,α′-dimercaptoglutaric acid to α,α′-dimethylglutaric acid has been established by means of X-ray powder photographs and thereby a connection is given to the glyceric aldehyde system (formulae p. 462).

A quasi-racemate has been obtained between (+)-thiophane-2,5-dicarboxylic acid and (−)-1,2-dithiolane-3,5-dicarboxylic acid. The possibility of replacing CH_2–CH_2 by S–S is directly connected with the *cis* conformation of the S–S group and the nearly planar structure of the 1,2-dithiolane ring.

The structure of some cyclic polysulphides has been discussed. The improbability of branched sulphur chains is pointed out referring to results obtained by means of UV and IR absorption and polarography.

The special character of the 1,2-dithiolane ring as determined by the above methods in comparison with disulphides in general should finally be stressed.

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